

EDITORIAL

Investigating the Vascular Influences of Sepsis in Portal Hypertension: Better Late Than Never?

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Endotoxin is a lipopolysaccharide (LPS) constituent of the cell wall of Gram-negative bacteria. During severe bacterial infection with endotoxemia and sepsis, the hemodynamic condition can be severely dampened due to the altered myocardial and vascular function. Previous animal experiments have yielded controversial results with regard to the influence of endotoxin on vascular function. For instance, endotoxin elicited a decrease in vascular pressure and resistance in the systemic circulation and, at the same time, an increase in vascular resistance in the pulmonary circulation of rats.¹ In LPS-treated rabbits, vascular hyporesponsiveness to norepinephrine was found in the ear artery, a peripheral large artery, but not in the renal vasculature, a resistance vascular bed.²

Endotoxemia is a well-known phenomenon in liver cirrhosis because of the impaired ability of Kupffer cells to remove gut-derived endotoxin. Furthermore, endotoxin is prone to get into the systemic circulation via the portal-systemic collateral vascular bed, the unique vasculature that develops in an attempt to divert the stagnant portal blood flow. A cytokine cascade with vasoactive substance release can be triggered by bacterial infection and endotoxemia, which leads to an increase in variceal pressure, impaired hemostasis, and a tendency to variceal hemorrhage.³ In addition, endotoxemia in cirrhotic rats with ascites can stimulate formation of nitric oxide (NO; a vascular endothelium-derived vasodilatory substance), directly or indirectly via cytokine cascade.⁴ It has been demonstrated that NO contributes to splanchnic vascular hyporesponsiveness to vasoconstrictors in portal hypertensive rats with acute hemorrhage.⁵ In fact, a previous study has indicated that bacterial infection is the single identifiable risk factor for rebleeding after endoscopic treatment for variceal hemorrhage in cirrhotic patients.⁶ A randomized trial

has further demonstrated that antibiotic prophylaxis after endoscopic therapy prevented rebleeding and decreased the amount of blood transfused for patients with acute gastroesophageal variceal hemorrhage.⁷

Clarification of the vascular derangements induced by bacterial infection, therefore, is a prerequisite to overcome the adverse impacts of sepsis in cirrhosis and portal hypertension. With the aim of investigating the vascular responsiveness modified by sepsis, Liao et al designed a series of experiments to survey the relevant influences.⁸ They found that, compared with the baseline portal hypertensive group, cecum ligation and puncture (CLP; an animal model of sepsis) elicited enhanced NO production and poorer superior mesenteric arterial vascular responsiveness at 6 and 18 hours after CLP. This finding was supported by evidence of increased plasma concentrations of $\text{NO}_3^-/\text{NO}_2^-$ (the relatively stable metabolite of NO) 6 hours after initiation of CLP. Such vascular hyporeactivity was corrected by L-nitro-arginine methyl ester plus 1400W [N-(3-(aminomethyl) benzyl) acetamidine hydrochloride, a selective inducible NO synthase (iNOS) inhibitor]. However, prophylactic imipenem did not alter NO production or vascular contractility after sepsis induced by CLP. The authors suggested that a higher dose of antibiotics and longer duration of treatment might be required.

During sepsis, the vascular responsiveness can vary in different vascular beds. Among these, the portal-systemic collateral vascular bed is also worth investigating because the results might be applied to gastroesophageal varices, the most prominent collateral vasculature in cirrhotic patients. In our previous study, an *in situ* collateral perfusion model was used to survey the alteration of collateral vascular reactivity to LPS in portal hypertensive rats. To our surprise, LPS elicited time-dependent portal-systemic collateral vascular



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responsiveness to arginine vasopressin (AVP).⁹ Compared with saline-injected portal-vein-ligated rats, decreased perfusion pressure change (i.e. a poorer vasoconstrictive response to AVP) occurred 30 minutes after LPS injection. However, higher perfusion pressure changes that denoted enhanced AVP response developed at 90 minutes, and were further aggravated 5 hours post-LPS. This is consistent with a previous study that showed an increased vasoconstrictive response to AVP in rat cremaster muscle microvessels at 90 minutes after induction of endotoxemia.¹⁰ Taking systemic hemodynamics into consideration, compared with the saline-injected group, when tachycardia that suggested early-stage shock developed (90 minutes post-LPS injection), the initial poorer vasoconstrictive AVP response at 30 minutes turned out to be stronger. That is, when systemic hypotension ensued at 5 hours, the AVP response was exaggerated.⁹ These results raised our interest in whether or not, in endotoxemic shock, the portal-systemic collaterals, like most resistance vessels, constrict in an attempt to compensate for systemic hypotension and divert their blood flow to vital tissues. Liao et al⁸ showed that the poorer superior mesenteric arterial vascular responsiveness developed at 6 hours and 18 hours after CLP in portal hypertensive rats. The various time-dependent changes might have been related to different experimental designs for different vascular beds. Nevertheless, they reflect the complexity of vascular response alteration with the progression of sepsis.

Liao et al⁸ also reported enhanced NO production 6 hours after initiation of CLP-induced sepsis in portal hypertensive rats, as compared with control portal hypertensive rats without sepsis. In our recent survey,⁹ we found that portal hypertensive rats, 30 minutes post-LPS administration, had higher splenorenal shunting (the most prominent intra-abdominal portal-systemic collateral vessel) and endothelial NOS expression than the control group with saline injection. At 90 minutes and 5 hours post-injection, enhanced splenorenal shunt iNOS and endothelin-1 expression (a vascular endothelium-derived potent vasoconstrictive substance) were observed in the LPS group. Liao et al⁸ also indicated that the augmented NO overproduction by iNOS resulted in further vascular hyporesponsiveness in portal vein-ligated rats 6 hours after CLP. Taken together, these results indicate that iNOS plays a major

role in increased NO production at this stage after the induction of sepsis.

Because portal hypertensive and cirrhotic patients are frequently afflicted by endotoxemia, bacterial translocation and sepsis, the clarification of vascular responsiveness in sepsis does contribute much to a better control of gastroesophageal variceal bleeding. However, more data are urgently required to clarify the whole course and to build up the mechanism. Although it might not be possible to extrapolate the results of animal studies to clinical practice at present, accumulating evidence is paving the way.

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